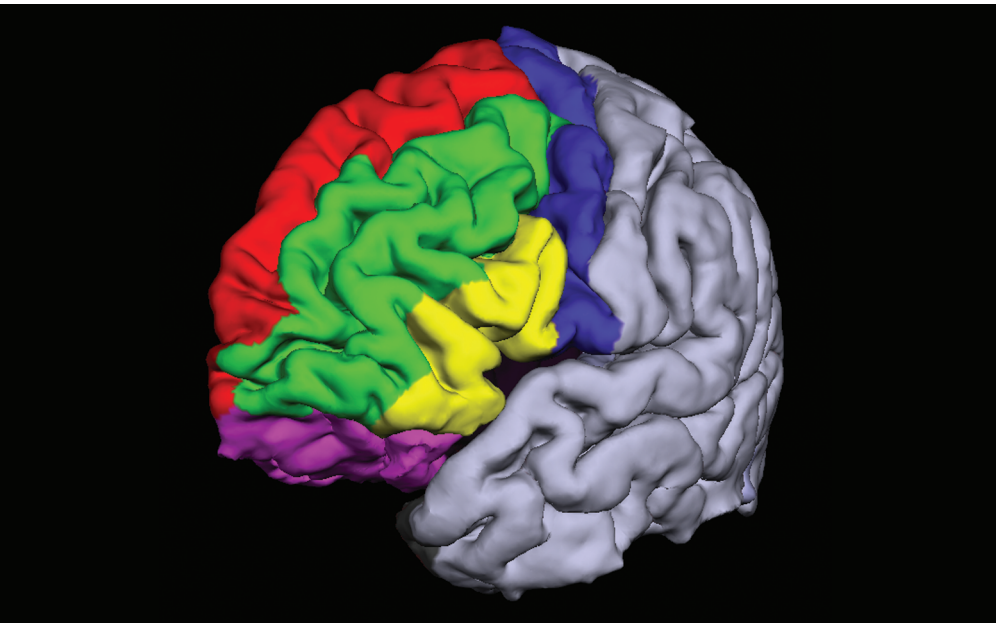
Research to Practice



Clinical Applications of Neuroimaging for Treating Depressive Disorders

by Steven D. Targum, MD, and Dan V. Iosifescu, MD, MSc

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INTRODUCTION

It is well documented that the currently available antidepressants achieve only partial clinical response in many patients with major depressive disorder (MDD) and that approximately 25 to 35 percent of MDD patients actually achieve full remission of symptoms. One reason for the apparent limited clinical efficacy is that different biological-functional deficits may be subsumed under the broad classification of MDD as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*). Recently, neuroimaging research has focused on the identification of distinct biological subtypes within this broad spectrum of MDD, which might have distinctly different patterns of clinical response as well. In fact, the application of neuroimaging techniques to study MDD has yielded some intriguing possibilities related to differential diagnosis, the prediction of treatment response, and even the prediction of placebo response. In this column, I interviewed Dan V. Iosifescu, MD, MSc, who is Assistant Professor of Psychiatry at the Harvard Medical School, and Director of Translational Neuroscience and Site Director for the Bipolar Trials Network at the Massachusetts General Hospital in Boston, Massachusetts.

WHAT CLINICAL VALUE CAN NEUROIMAGING STUDIES OFFER CLINICIANS WHO TREAT MOOD DISORDERS?

Dr. Iosifescu: I believe that neuroimaging studies may become very valuable in several respects. First, they can offer insights into the neurobiology of mood disorders and reveal reliable pathophysiological markers that may be associated with specific subtypes of mood disorders. These findings could eventually translate into objective diagnostic criteria. Second, specific changes measured with neuroimaging can be associated with treatment response; this could translate into tests that would help the clinical selection of next-step treatment in patients who failed previous antidepressant trials. Moreover, the discovery of disease-specific structural or functional deficits could help our understanding of disease development and thereby guide more accurate clinical diagnoses and even drug development.

But, I need to emphasize that none of these uses of neuroimaging has been sufficiently validated to warrant current application in clinical practice, although the long-term promise of such studies remains extraordinary.

ARE THERE SPECIFIC BRAIN REGIONS ASSOCIATED WITH THE SYMPTOMS OF MDD?

Dr. Iosifescu: Yes. Specifically, the limbic and prefrontal cortical regions of the brain are associated with the behavioral and functional deficits seen in MDD patients. These regions are very important for emotional regulation in healthy individuals also. In depressed subjects, there appears to be a functional imbalance in the role and activity between the limbic regions (such as the amygdala and hippocampus that are believed to

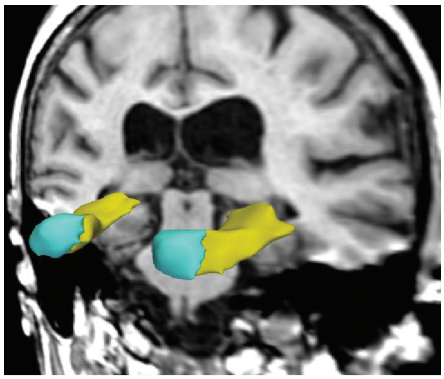

FIGURE 1. Hippocampus and amygdala. blue=amygdala, yellow=hippocampus

mediate emotional and stress responses) (Figure 1) and the prefrontal cortical regions like the posterior orbital cortex and anterior cingulate gyrus that modulate emotional expression.[1] The accumulating evidence from numerous structural and functional imaging studies as well as magnetic resonance spectroscopy (MRS) points to an imbalance in brain circuitry in patients with MDD, where the excessive activity in the limbic system is not adequately modulated and controlled by hypoactive prefrontal areas.

WHERE HAVE STRUCTURAL BRAIN CHANGES BEEN ASSOCIATED WITH MOOD DISORDERS?

Dr. Iosifescu: So far, the neuroanatomical abnormalities associated with MDD include morphological lesions in frontal lobe regions like the anterior cingulate gyrus, the hippocampus, and white matter lesions (WML) as well (Figure 2).[2-4] For instance, reduced hippocampal volume has been reported in first-episode depression and depressed pediatric patients suggesting it is not a drug effect. Furthermore, progressive reductions in hippocampal size have been reported in patients with chronic, untreated depression as well.[5]

WHAT IS THE CLINICAL SIGNIFICANCE OF THE WHITE MATTER LESIONS?

Dr. Iosifescu: It is possible that the abnormal white matter connections between the limbic and prefrontal cortical structures may contribute to the imbalance in brain circuitry that I mentioned before. Not surprisingly, these WMLs (which represent areas of demyelination) are more frequently found in elderly depressed patients and have been associated with a distinct subtype of illness called "vascular depression," which appears to be less responsive to antidepressants compared with MDD patients with no WML. Nonetheless, WML at any age may disrupt brain circuitry patterns and might be predictive of poor treatment response.[4]

WHAT FUNCTIONAL NEUROIMAGING TECHNIQUES HAVE BEEN USED TO STUDY MDD PATIENTS?

Dr. Iosifescu: Researchers have used a variety of functional techniques to study brain activity in depression, including single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). All of these functional techniques assess changes in cerebral blood flow (CBF) or glucose metabolism, which in turn suggest what brain areas are hyper- or hypoactive. A very exciting part of these studies involve measuring changes in CBF or metabolism actively during specific emotional or cognitive tasks. Compared to healthy controls, MDD patients show different functional patterns when they are exposed to anger induction, emotional faces, or even sad words.

These PET studies have demonstrated abnormally increased or decreased CBF in specific limbic and prefrontal cortical structures. Remarkably, the metabolic abnormalities revealed by these PET studies actually improve with antidepressant treatment.[6] Beyond that, some studies have shown that the metabolic abnormalities do not improve in treatment nonresponders and reveal a different pattern of activation in placebo responders.[7] Overall, these preliminary studies suggest that it may eventually be possible to predict and to differentiate between true antidepressant response and placebo response in MDD.

ARE THERE CLINICAL APPLICATIONS FOR MAGNETIC RESONANCE SPECTROSCOPY IN MDD?

Dr. Iosifescu: MRS is a noninvasive tool for *in-vivo* chemical analysis, which can be used to compare brain levels of several neurochemicals and specific metabolic pathways. This represents a more refined analysis of metabolism compared to SPECT or PET, which measure CBF or glucose metabolic rates. MRS has been used in psychiatry to measure brain neurotransmitters like GABA and glutamate, structural components like synaptic proteins, and even brain levels of psychotropic drugs.[8] To date, Proton (1H) MRS studies have reported decreased levels of GABA and glutamate in MDD patients (which seem to be corrected by adequate treatment) and impairment of cellular membrane phospholipid metabolism. Phosphorus (31P) MRS studies have suggested deficits of brain energy metabolism in depression, which may be related to a mitochondrial dysfunction. More recently, we reported that response to antidepressant treatment is associated with a renormalization of bioenergetic metabolism.[9] This metabolic measure can differentiate between responders and nonresponders and may suggest new potential avenues for antidepressant treatment (such as substances which increase

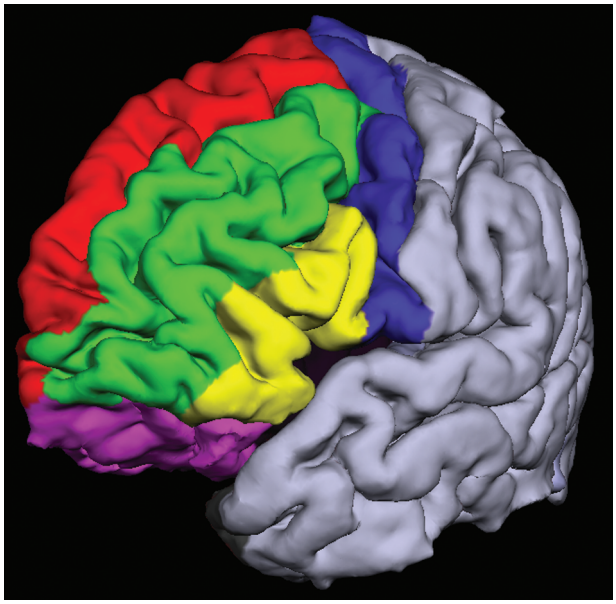

FIGURE 2. Frontal lobe areas. red=superior frontal gyrus, green=middle frontal gyrus, yellow=inferior frontal gyrus, violet=orbital cortex, dark blue=precentral gyrus

mitochondrial activity). In sum, I think that MRS may eventually have practical use in the clinic to target specific chemical markers to predict treatment response for MDD patients.

WHAT IS ON THE HORIZON FOR THE USE OF NEUROIMAGING IN THE EVALUATION AND TREATMENT OF MDD PATIENTS?

Dr. Iosifescu: As I have mentioned, I believe that structural and functional neuroimaging and MRS techniques will eventually be useful in the clinic for differential diagnosis and selection of appropriate antidepressant treatments. It is possible that these techniques will also identify likely placebo responders who might not need antidepressants at all. These tools will help us to move from mere clinical description to a genuine clinical-neuropathological correlation in our approach to depressed patients.

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FINANCIAL DISCLOSURES: Dr. Targum has stock or stock options in BrainCells Inc. and Prana Biotechnology Ltd. In the past year, Dr. Targum has been a consultant to United BioSource Corporation, Dynogen, Epix, DOV Pharmaceuticals, Sepracor, NuPathe, and Memory Pharmaceuticals. Dr. Iosifescu has received research support from Aspect Medical Systems, Forest Laboratories, and Janssen Pharmaceutica; he has been a consultant for Forest Laboratories, Gerson Lehrman Group, and Pfizer, Inc., and he has been a speaker for Cephalon, Inc., Eli Lilly & Co., Forest Laboratories, Pfizer, Inc. and Reed Medical Education (a company working as a logistics collaborator for the MGH Psychiatry Academy). The education programs conducted by the MGH Psychiatry Academy were supported through Independent Medical Education (IME) grants from pharmaceutical companies co-supporting programs along with participant tuition. For 2008, those companies included Astra Zeneca, Eli Lilly, and Janssen Pharmaceuticals.

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